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2. Patent application number *(The Patent Office will fill in this part)* 13 JUN 2003

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

The Babraham Institute
Babraham Hall
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United Kingdom

Patents ADP number *(if you know it)*

7414589002

If the applicant is a corporate body, give the country/state of incorporation: United Kingdom

4. Title of the invention: Differential Gene Expression in Schizophrenia

5. Full name, address and postcode in the United Kingdom to which all correspondence relating to this form and translation should be sent

Reddie & Grose
16 Theobalds Road
LONDON
WC1X 8PL

91001

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Differential Gene Expression in Schizophrenia

This invention relates to methods of identifying potential therapeutic agents for the prevention, treatment, or amelioration of schizophrenia (SZ), to methods of diagnosis of schizophrenia, and to methods of prevention, treatment, or amelioration of schizophrenia.

SZ is a severe psychiatric disorder characterized by hallucinations, delusions, disorganized thought, and various cognitive impairments. Polygenic models of inheritance and linkage analysis studies have postulated that several genes confer susceptibility to SZ. Hakak *et al* (PNAS, 2001, 98 (8) 4746-4751) have reported that the expression levels of genes involved in neuronal myelination, development, synaptic plasticity, neurotransmission, and signal transduction were altered in the dorsolateral prefrontal cortex of SZ brain tissue. Mimmack *et al* (PNAS, 2002, 99 (7) 4680-4685) have found significant up-regulation of several members of the apolipoprotein L family in the prefrontal cortex of schizophrenia brains. Middleton *et al* (Journal of Neuroscience, 2002, 22 (7) 2718-2729) have identified alterations of specific metabolic pathways in schizophrenia. However, the molecular basis of schizophrenia is only beginning to be understood. This has hampered development of effective treatments for schizophrenia, and reliable diagnosis of the disorder.

We have identified abnormalities in the expression levels of several genes in the prefrontal cortex of patients with schizophrenia compared with control samples. In particular, the expression level of the following genes was observed to be decreased in the prefrontal cortex of schizophrenia patients:

PARG;OLR1; ARPC3; ARPC3; DNCLI1; PPM1A; ATPIF1; TIMM17A; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; FLJ13611; HIRIP5; TAC1; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1;

Ornithine related genes: OAT; OAZIN; OAZ2;

Arginine related genes: ARG2;

ATP synthase (mitochondrial) genes: ATP6V1B2; ATP6IP2; ATP6V1C1;

ATP synthase (vacuolar) genes: ATP5J; ATP5G3; ATP5L; ATP5C1; ATP5F1; ATP5A1;

Complex 1 genes: NDUFA5; NDUFA6; NDUFAB1; NDUFB3; NDUFB6; NDUFB5; NDUFB1; NDUFS4; NDUFA4; NDUFC2; NDUFB4;

Complex 3 genes: UQCRH; UQCRFS1; UQCRC2; UQCRB; UQCRC2;

Complex 4 genes: COX7A2; COX7B; COX5A; COX17; COX11; COX7CP1; COX7BP1;

Holocytochrome c Synthetase genes: HCCS;

Adenine translocators genes: SLC25A4

Voltage dependent anion channels (in mitochondrial outer-membrane) genes: VDAC2; VDAC1P; VDAC3;

Lactate metabolism genes: LDHB; LDHA;

Isocitrate dehydrogenase genes: IDH3B; IDH3A

HMG related genes: HMGCR

Glutamate metabolism genes: GLRX2.

The expression level of the following genes was observed to be increased in the prefrontal cortex of schizophrenia patients:

FBS1; WFS1; PRODH; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-REN-24; TXNL2; SOD3; BCAT2;

purine metabolism (matrix) genes: ALDH4A1; PYCR1;

metallo proteins genes: MT1X; MT1L; MT1G; MT1H; MT2A; MT1E; MT1F;

Arginine related genes: DDAH2;

Glycine/Serine metabolism genes: AMT;

HMG related genes: HMGCL;

Oxide related genes: EPHX1.

Table 1 gives the fold changes in expression of the above genes in the prefrontal cortex of schizophrenia brains compared with control samples, and includes Unigene, ReSeq, and Genbank details, and descriptions of the genes, including synonyms.

Many of the changes are mitochondrial changes. These are illustrated schematically in Figure 1. The changes include changes in ROS stress systems (see the Example).

We have appreciated that these abnormalities can be used to identify potential therapeutic agents for the prevention, treatment, or amelioration of schizophrenia, and for the diagnosis of schizophrenia or susceptibility to schizophrenia.

According to the invention there is provided use of any of the following in a screening assay to identify a potential therapeutic agent for the prevention, treatment, or amelioration of schizophrenia:

(i) proteins encoded by the following genes: PARG;OLR1; ARPC3; ARPC3; DNCLI1; PPM1A; ATPIF1; TIMM17A; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; FLJ13611; HIRIP5; TAC1; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1; OAT; OAZIN; OAZ2; ARG2; ATP6V1B2; ATP6IP2; ATP6V1C1; ATP5J; ATP5G3; ATP5L; ATP5C1; ATP5F1; ATP5A1; NDUFA5; NDUFA6; NDUFAB1; NDUFB3; NDUFB6; NDUFB5; NDUFB1; NDUFS4; NDUFA4; NDUFC2; NDUFB4; UQCRH; UQCRFS1; UQCRC2; UQCRB; UQCRC2; COX7A2; COX7B; COX5A; COX17; COX11; COX7CP1; COX7BP1; HCCS; SLC25A4; VDAC2; VDAC1P; VDAC3; LDHB; LDHA; IDH3B; IDH3A; HMGCR; GLRX2; FBS1; WFS1; PRODH; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-REN-24; TXNL2; SOD3; BCAT2; ALDH4A1; PYCR1; MT1X; MT1L; MT1G; MT1H; MT2A; MT1E; MT1F; DDAH2; AMT; HMGCL; EPHX1; or ii) nucleic acid encoding any of the proteins of (i) above.

There is also provided according to the invention use of a regulator of expression of any of (i) above, in a screening assay to identify a potential therapeutic agent for the prevention, treatment, or amelioration of schizophrenia.

There is further provided according to the invention use of a binding partner of any of (i) above in a screening assay to identify a potential therapeutic agent for the prevention, treatment, or amelioration of schizophrenia.

According to the invention there is also provided use of an expression vector comprising nucleic acid encoding any of (i) above in a screening assay to identify a potential therapeutic agent for the prevention, treatment, or amelioration of schizophrenia.

There is further provided according to the invention use of a cell or cell line expressing nucleic acid encoding any of (i) above in a screening assay to identify a potential therapeutic agent for the prevention, treatment, or amelioration of schizophrenia. Preferably the cell is a neural cell, or an oligodendrocyte.

There is also provided according to the invention a recombinant mouse in which expression of a gene encoding any of the proteins of (i) above is altered compared with expression of the corresponding gene in normal mice. Preferably

expression of two or more of the genes is altered. Expression of the gene or genes in the recombinant mouse may be increased or decreased. Where expression is decreased, preferably the mouse is a knockout mouse for the gene or genes.

Preferably expression of PARG;OLR1; ARPC3; ARPC3; DNCLI1; PPM1A; ATPIF1; TIMM17A; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; FLJ13611; HIRIP5; TAC1; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1; OAT; OAZIN; OAZ2; ARG2; ATP6V1B2; ATP6IP2; ATP6V1C1; ATP5J; ATP5G3; ATP5L; ATP5C1; ATP5F1; ATP5A1; NDUFA5; NDUFA6; NDUFAB1; NDUFB3; NDUFB6; NDUFB5; NDUFB1; NDUFS4; NDUFA4; NDUFC2; NDUFB4; UQCRH; UQCRFS1; UQCRC2; UQCRB; UQCRC2; COX7A2; COX7B; COX5A; COX17; COX11; COX7CP1; COX7BP1; HCCS; SLC25A4; VDAC2; VDAC1P; VDAC3; LDHB; LDHA; IDH3B; IDH3A; HMGCR; GLRX2 is decreased in the recombinant mouse.

Preferably expression of FBS1; WFS1; PRODH; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-REN-24; TXNL2; SOD3; BCAT2; ALDH4A1; PYCR1; MT1X; MT1L; MT1G; MT1H; MT2A; MT1E; MT1F; DDAH2; AMT; HMGCL; EPHX1 is increased in the recombinant mouse.

The invention also provides use of a recombinant mouse of the invention as an animal model for schizophrenia.

According to the invention there is also provided use of a mouse of the invention, or cells obtained or derived from the mouse, in a screening assay to identify a potential therapeutic agent for the prevention, treatment, or amelioration of schizophrenia.

A screening assay for identifying a potential therapeutic agent for the prevention, treatment, or amelioration of schizophrenia may comprise screening for a modulator of expression of a gene encoding any of the proteins of (i) above by: providing a system capable of expressing a gene encoding any of the proteins of (i) above; maintaining the system under conditions for expression of the gene in the presence and absence of a candidate modulator of expression of the gene; and determining the expression level of the gene in the presence and absence of the candidate modulator.

An upregulator of expression of any of the following is expected to provide a potential therapeutic agent for the prevention, treatment, or amelioration of

schizophrenia: PARG;OLR1; ARPC3; ARPC3; DNCLI1; PPM1A; ATPIF1; TIMM17A; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; FLJ13611; HIRIP5; TAC1; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1; OAT; OAZIN; OAZ2; ARG2; ATP6V1B2; ATP6IP2; ATP6V1C1; ATP5J; ATP5G3; ATP5L; ATP5C1; ATP5F1; ATP5A1; NDUFA5; NDUFA6; NDUFAB1; NDUFB3; NDUFB6; NDUFB5; NDUFB1; NDUFS4; NDUFA4; NDUFC2; NDUFB4; UQCRH; UQCRFS1; UQCRC2; UQCRB; UQCRC2; COX7A2; COX7B; COX5A; COX17; COX11; COX7CP1; COX7BP1; HCCS; SLC25A4; VDAC2; VDAC1P; VDAC3; LDHB; LDHA; IDH3B; IDH3A; HMGCR; GLRX2.

A downregulator of expression of any of the following is expected to provide a potential therapeutic agent for the prevention, treatment, or amelioration of schizophrenia: FBS1; WFS1; PRODH; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-REN-24; TXNL2; SOD3; BCAT2; ALDH4A1; PYCR1; MT1X; MT1L; MT1G; MT1H; MT2A; MT1E; MT1F; DDAH2; AMT; HMGCL; EPHX1.

An alternative screening assay for identifying a potential therapeutic agent for the prevention, treatment, or amelioration of schizophrenia may comprise screening for a regulator of the activity of any of the proteins of (i) above by: contacting the protein with a candidate regulator and determining the activity of the protein in the presence and absence of the candidate regulator.

An enhancer or activator of the activity of any of the following proteins may provide a potential therapeutic agent for the prevention, treatment, or amelioration of schizophrenia: PARG;OLR1; ARPC3; ARPC3; DNCLI1; PPM1A; ATPIF1; TIMM17A; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; FLJ13611; HIRIP5; TAC1; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1; OAT; OAZIN; OAZ2; ARG2; ATP6V1B2; ATP6IP2; ATP6V1C1; ATP5J; ATP5G3; ATP5L; ATP5C1; ATP5F1; ATP5A1; NDUFA5; NDUFA6; NDUFAB1; NDUFB3; NDUFB6; NDUFB5; NDUFB1; NDUFS4; NDUFA4; NDUFC2; NDUFB4; UQCRH; UQCRFS1; UQCRC2; UQCRB; UQCRC2; COX7A2; COX7B; COX5A; COX17; COX11; COX7CP1; COX7BP1; HCCS; SLC25A4; VDAC2; VDAC1P; VDAC3; LDHB; LDHA; IDH3B; IDH3A; HMGCR; GLRX2.

An inhibitor of the activity of any of the following proteins may provide a potential therapeutic agent for the prevention, treatment, or amelioration of schizophrenia: FBS1; WFS1; PRODH; AMT; CLN3; ACOX1; G6PD; GCDH;

COL5A1; NY-REN-24; TXNL2; SOD3; BCAT2; ALDH4A1; PYCR1; MT1X; MT1L; MT1G; MT1H; MT2A; MT1E; MT1F; DDAH2; AMT; HMGCL; EPHX1.

A further screening assay for identifying a potential therapeutic agent for the prevention, treatment, or amelioration of schizophrenia may comprise screening for a regulator of the interaction of any of the proteins of (i) above with a binding partner required for the biological effect of the protein by: contacting the protein with the binding partner in the presence of a candidate regulator, and determining binding of the protein to its binding partner in the presence and absence of the candidate regulator.

An enhancer or activator of the interaction of any of the following proteins with a binding partner required for the biological effect of the protein may provide a potential therapeutic agent for the prevention, treatment, or amelioration of schizophrenia: PARG;OLR1; ARPC3; ARPC3; DNCLI1; PPM1A; ATPIF1; TIMM17A; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; FLJ13611; HIRIP5; TAC1; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1; OAT; OAZIN; OAZ2; ARG2; ATP6V1B2; ATP6IP2; ATP6V1C1; ATP5J; ATP5G3; ATP5L; ATP5C1; ATP5F1; ATP5A1; NDUFA5; NDUFA6; NDUFAB1; NDUFB3; NDUFB6; NDUFB5; NDUFB1; NDUFS4; NDUFA4; NDUFC2; NDUFB4; UQCRH; UQCRFS1; UQCRC2; UQCRB; UQCRC2; COX7A2; COX7B; COX5A; COX17; COX11; COX7CP1; COX7BP1; HCCS; SLC25A4; VDAC2; VDAC1P; VDAC3; LDHB; LDHA; IDH3B; IDH3A; HMGCR; GLRX2.

An inhibitor of the interaction of any of the following proteins with a binding partner required for the biological effect of the protein may provide a potential therapeutic agent for the prevention, treatment, or amelioration of schizophrenia: FBS1; WFS1; PRODH; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-REN-24; TXNL2; SOD3; BCAT2; ALDH4A1; PYCR1; MT1X; MT1L; MT1G; MT1H; MT2A; MT1E; MT1F; DDAH2; AMT; HMGCL; EPHX1.

A further screening assay for identifying a potential therapeutic agent for the prevention, treatment, or amelioration of schizophrenia may comprise screening for a binding partner of any of the proteins of (i) above by: contacting the protein with a sample comprising a candidate binding partner, and determining whether the candidate binding partner binds to the protein.

There is also provided according to the invention a method of diagnosing whether a subject has, or is at risk of developing schizophrenia, which comprises determining the level of any of the proteins of (i) above, or the expression level of a gene encoding any of the proteins of (i) above, in a biological sample obtained from the subject, or in a sample derived from a biological sample obtained from the subject.

The biological sample may comprise any of the following: CNS tissue, brain tissue, cells isolated from the prefrontal cortex, cells isolated from the developing neuroepithelium; a neural stem cell; a progenitor cell.

Cells isolated from the developing human neuroepithelium can be isolated in culture and grown as aggregates termed neurospheres (Svendsen CN, and Smith AG, *Trends Neurosci* 1999 Aug; 22(8): 357-64). These contain a mixture of neural stem and progenitor cells, can be propagated in culture for extended time periods, and hold potential as a source of tissue for repairing the damaged CNS. According to the invention, the sample derived from the biological sample may be a neurosphere.

Preferably the biological sample comprises peripheral tissue or a peripheral cell type in which the level of the protein, or the expression level of the gene, correlates with the level of the corresponding protein, or the expression level of the corresponding gene, in the prefrontal cortex.

Suitable peripheral tissue may comprise blood (consisting of plasma and blood cells). It is possible that a correlated level of protein, or correlated gene expression, may occur in one or more types of blood cell but not in others. In this case, it may be necessary to use blood cells of that type, or those types, which have been separated at least from some of the types of blood cells that do not have correlated levels or correlated expression. If a correlated level of protein, or correlated gene expression, occurs in more than one type of blood cell, blood cells of each type could be separated and, if necessary, pooled together for the determination.

A correlated level of protein, or correlated gene expression may occur in erythrocytes (red cells), platelets, or leukocytes (granulocytes: neutrophils, eosinophils, or basophils; or lymphoid cells: lymphocytes or monocytes).

Methods of determining the expression level of a gene are well known to those of ordinary skill in the art. For example, this may be achieved by determining the level of mRNA or protein expressed from the gene in the biological sample.

Examples of suitable methods for determining the level of mRNA expression are quantitative PCR (in particular, real-time quantitative PCR) performed on cDNA produced by reverse transcription of the mRNA, and Northern blotting.

In a preferred method of determining the level of mRNA expressed, total RNA is obtained from the biological sample, cDNA is synthesized from mRNA of the gene, and the cDNA is used for real-time quantitative PCR analysis to determine the level of the mRNA in the sample.

Examples of suitable methods for determining the level of protein expression are Western blotting and enzyme-linked immunosorbent assay (ELISA).

A binding partner of an expression product of the gene, may be used to detect the level of that expression product. The binding partner may be a protein, preferably an antibody or antibody fragment. The antibody or antibody fragment should bind specifically to the expression product so that the level of the expression product in the biological sample can be determined.

The binding partner may be a nucleic acid capable of hybridizing to a nucleic acid expression product of the gene. The nucleic acid should hybridize specifically (for example under conditions of high stringency) to the nucleic acid expression product so that the level of the nucleic acid expression product in the biological sample can be determined. A preferred nucleic acid binding partner is an oligonucleotide primer for the synthesis of cDNA by reverse transcription from mRNA of the gene.

The level of a nucleic acid expression product of the gene is preferably determined by amplification of that nucleic acid expression product, for example by PCR. Thus, primers capable of amplifying the nucleic acid expression product are provided. Nucleic acid capable of hybridizing (preferably under conditions of high stringency) to nucleic acid that is complementary to a nucleic acid expression product of the gene and/or nucleic acid which is a binding partner (preferably under conditions of high stringency) of an expression product of the gene may be used to amplify a nucleic acid expression product of the gene, for example to detect an expression product of the gene.

There is also provided a kit for the diagnosis of schizophrenia that comprises a means for detecting the protein or expression product of a gene encoding the protein. The detecting means may comprise a binding partner of the protein, and/or a nucleic

acid capable of hybridizing to nucleic acid that is complementary to a nucleic acid expression product of the gene.

There is also provided according to the invention a method of diagnosing whether a subject has, or is at risk of developing schizophrenia, which comprises determining the level of any of the proteins of (i), or the expression level of a gene encoding any of the proteins of (i) above, in the brain (preferably the prefrontal cortex) of the subject.

The level of more than one of the proteins of (i) above, or the expression level of more than one of the genes encoding the proteins of (i) above may be determined. This may increase the accuracy of the diagnosis.

If the level of the protein or expression product in the brain is abnormal, the subject is diagnosed as either having schizophrenia, or being at risk of developing schizophrenia.

In particular, the subject is diagnosed as either having schizophrenia, or being at risk of developing schizophrenia, if the level of any of the following proteins, or the expression level of a gene encoding any of the following proteins is reduced compared to a normal subject: PARG;OLR1; ARPC3; ARPC3; DNCLI1; PPM1A; ATPIF1; TIMM17A; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; FLJ13611; HIRIP5; TAC1; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1; OAT; OAZIN; OAZ2; ARG2; ATP6V1B2; ATP6IP2; ATP6V1C1; ATP5J; ATP5G3; ATP5L; ATP5C1; ATP5F1; ATP5A1; NDUFA5; NDUFA6; NDUFAB1; NDUFB3; NDUFB6; NDUFB5; NDUFB1; NDUFS4; NDUFA4; NDUFC2; NDUFB4; UQCRH; UQCRFS1; UQCRC2; UQCRB; UQCRC2; COX7A2; COX7B; COX5A; COX17; COX11; COX7CP1; COX7BP1; HCCS; SLC25A4; VDAC2; VDAC1P; VDAC3; LDHB; LDHA; IDH3B; IDH3A; HMGCR; GLRX2.

The subject is diagnosed as either having schizophrenia, or being at risk of developing schizophrenia, if the level of any of the following proteins, or the expression level of a gene encoding any of the following proteins is increased compared to a normal subject: FBS1; WFS1; PRODH; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-REN-24; TXNL2; SOD3; BCAT2; ALDH4A1; PYCR1; MT1X; MT1L; MT1G; MT1H; MT2A; MT1E; MT1F; DDAH2; AMT; HMGCL; EPHX1.

There is further provided according to the invention a method of prevention, treatment, or amelioration of schizophrenia which comprises increasing the level or activity of any of the following proteins in the brain (in particular the prefrontal cortex) of a subject in need of such prevention, treatment, or amelioration: PARG;OLR1; ARPC3; ARPC3; DNCLI1; PPM1A; ATPIF1; TIMM17A; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; FLJ13611; HIRIP5; TAC1; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1; OAT; OAZIN; OAZ2; ARG2; ATP6V1B2; ATP6IP2; ATP6V1C1; ATP5J; ATP5G3; ATP5L; ATP5C1; ATP5F1; ATP5A1; NDUFA5; NDUFA6; NDUFAB1; NDUFB3; NDUFB6; NDUFB5; NDUFB1; NDUFS4; NDUFA4; NDUFC2; NDUFB4; UQCRH; UQCRFS1; UQCRC2; UQCRB; UQCRC2; COX7A2; COX7B; COX5A; COX17; COX11; COX7CP1; COX7BP1; HCCS; SLC25A4; VDAC2; VDAC1P; VDAC3; LDHB; LDHA; IDH3B; IDH3A; HMGCR; GLRX2.

There is also provided according to the invention a method of prevention, treatment, or amelioration of schizophrenia which comprises reducing the level or activity of any of the following proteins in the brain (in particular the prefrontal cortex) of a subject in need of such prevention, treatment, or amelioration: FBS1; WFS1; PRODH; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-REN-24; TXNL2; SOD3; BCAT2; ALDH4A1; PYCR1; MT1X; MT1L; MT1G; MT1H; MT2A; MT1E; MT1F; DDAH2; AMT; HMGCL; EPHX1.

The level of a protein may be altered by gene therapy. The level of a protein may be altered by use of a regulator of expression of a gene coding for the protein.

Experiments which are the basis of the invention are described in the following example, with reference to the accompanying drawings in which:

Figure 1 shows mitochondrial changes associated with schizophrenia;

Figure 2 shows sample quality control steps;

Figure 3 shows data quality control steps;

Figures 4 and 5 show clustering analysis between control (C) and schizophrenia (S) samples; and

Figure 6 shows oxidative buffering.

Example

Integrating Transcriptomics, Proteomics, and Classical Genetics: Fishing in modern neuropsychiatric research

Affymetrix® GeneChip® Post-Mortem Brain Studies

HG-U133 set includes:

- 39,000 probes
- 33,000 annotated
- 2 chips: A and B
- Each w/ ~23,000 genes on 1.28 cm^2

Our Studies:

- 150 PM human brain samples from SMRI
- Completed on HG-U133A chips and continuing on B
- Extensive Quality Control(QC) steps
- Cluster analysis

Sample QC Steps (see Figure 2):

Total RNA is screened for degraded samples
cRNA is generated and screened for poor modal length

- Poor samples are run on Test3 GeneChips®
- Prisitine samples are run on U133 GeneChips®

Microarrays are put through our in-house Data QC screen and only "clean" data sets are retained, poor set samples are rerun or rejected

Data QC Steps (see Figure 3):

6 data filters

- RNA digestion plots
- Box plots
- 2 D-chip screens
- In-house parameter script
- In-house heuristic meta-analysis script

Data Mining

- Flag Filtering
- Fold Difference and Significance Filtering
- Subset Significant Gene Overlapping
- Pathway Specific Filtering

Cluster Analysis (see Figures 4 and 5)

Initial Clustering (17,886 genes)

Patients begin to separate ...

Until the trees begin to separate large groups of patients on a large gene scale (392 genes)

Filtering on oxidative stress and mitochondrial genes (35 genes)

- 82% separation for C in S
- 90% separation for S in C

Mitochondrial Involvement: Evidence for ROS stress (see Figure 6)

Oxidative Stress:
Evidence for Stress Response

Up-regulations in MT transcripts

Changes in specific ROS stress systems including:

- SOD's
- MSR
- GLRX
- PDCD's
- Specific RAS pathways
- HIF's
- Fe containing molecules

Changes in DNA repair mechanisms

Future Directions

- Continue data mining of Affymetrix® results
- Validate gene hits via Q-PCR and poly-"omics"
- Genotyping and SNP analysis of genes that separate patient groups
- GeneChip analysis of peripheral tissues including liver, spleen, blood and duramata

Table 1

Significant clustering 90% separation of schizophrenics from controls	Systematic	Common	Genbank	Map	UniGene	GeneSpring Norm Fold S		ttest S-C	Dchip Norm Fold S		ttest S-C	Description
	205080_at	PARG	NM_003631	10q11.23	Hs.91390	1.510748	Down	3.7332E-05	1.1881727	Down	0.0160033	Homo sapiens poly (ADP-ribose) glycohydrolase (PARG), mRNA.
	211682_s_at	VDAC2	L06886	10q22	Hs.78902	1.12617	Down	0.014133997	1.1240973	Down	0.0034869	Homo sapiens voltage-dependent anion channel 2 (VDAC2), mRNA.
	210004_at	OLR1; OLR1; LOX1; LOX-1; SCARE1	AF035776	12p13.2-p12.3	Hs.77729	1.377408	Down	0.004075548	1.2097276	Down	0.0027743	synonyms: LOX1, LOX-1, SCARE1; scavenger receptor class E, member 1; Homo sapiens oxidised low density lipoprotein (lectin-like) receptor 1 (OLR1), mRNA.
	208736_at	ARPC3; ARPC3; ARC21; p21-Arc	AF004551	12q24.11	Hs.293750	1.265561	Down	5.21013E-05	1.1353506	Down	0.0402548	synonyms: ARC21, p21-Arc; ARP2/3 protein complex subunit p21; Homo sapiens actin related protein 2/3 complex, subunit 3, 21kDa (ARPC3), mRNA.
	208909_at	UQCRFS1; UQCRFS1; RIS1	BC000649	19q12-q13.1	Hs.3712	1.168573	Down	0.01259279	1.2110709	Down	0.0002244	synonym: RIS1; Homo sapiens ubiquinol-cytochrome c reductase, Rieske iron-sulfur polypeptide 1 (UQCRFS1), nuclear gene encoding mitochondrial protein, mRNA.
	217976_s_at	DNCLI1	NM_016141		Hs.268483	1.334079	Down	6.56512E-05	1.2679291	Down	0.0003879	Homo sapiens dynein, cytoplasmic, light intermediate polypeptide 1 (DNCLI1), mRNA.

203986_s_at	PPM1A; PPM1A; PP2CA; MGC9201; PP2C-ALPHA	NM_021003		Hs.57764	1.331601	Down	3.751E-05	1.178799	Down	0.0028368	synonyms: PP2CA, PP2C-ALPHA, MGC9201; isoform 1 is encoded by transcript variant 1 and 3; protein phosphatase 2C alpha isoform; Homo sapiens protein phosphatase 1A (formerly 2C), magnesium-dependent, alpha isoform (PPM1A), transcript variant 1, mRNA; synonyms: PP2CA, PP2C-ALPHA, MGC9201; isoform 2 is encoded by transcript variant 2; protein phosphatase 2C alpha isoform; Homo sapiens protein phosphatase 1A (formerly 2C), magnesium-dependent, alpha isoform (PPM1A), transcript variant 2, mRNA; synonyms: PP2CA, PP2C-ALPHA, MGC9201; isoform 1 is encoded by transcript variant 1 and 3; protein phosphatase 2C alpha isoform; Homo sapiens protein phosphatase 1A (formerly 2C), magnesium-dependent, alpha isoform (PPM1A), transcript

218671_s_at	ATPIF1; ATPIF1; MGC1167; MGC8898	NM_016311	1p35.3	Hs.24133 6	1.168111	Down	0.0162928648	1.1558271	Down	0.0163928		synonyms: MGC8898, MGC1167, ATPI; isoform 1 is encoded by transcript variant 1; Homo sapiens ATPase inhibitory factor 1 (ATPIF1), transcript variant 1, nuclear gene encoding mitochondrial protein, mRNA.; synonyms: MGC8898, MGC1167, ATPI; isoform 2 is encoded by transcript variant 2; Homo sapiens ATPase inhibitory factor 1 (ATPIF1), transcript variant 2, nuclear gene encoding mitochondrial protein, mRNA.; synonyms: MGC8898, MGC1167, ATPI; isoform 3 is encoded by transcript variant 3; Homo sapiens ATPase inhibitory factor 1 (ATPIF1), transcript variant 3, nuclear gene encoding mitochondrial protein, mRNA.
219833_at	GLRX2; GLRX2; GRX2	NM_016066	1q31.2-q31.3	Hs.5054	1.214861	Down	0.000850748	1.237224	Down	0.0001632		synonym: GRX2; thioltransferase; contains nuclear membrane localisation; CGI-133 protein; Homo sapiens glutaredoxin 2 (GLRX2), mRNA.
215171_s_at	TIMM17A; TIMM17A; TIM17; TIM17A	AK023063	1q32.1	Hs.20716	1.223888	Down	0.0004227331	1.2024004	Down	0.0044235		synonyms: TIM17, TIM17A; preprotein translocase; Homo sapiens translocase of inner mitochondrial membrane 17 homolog A (yeast) (TIMM17A), mRNA.

210418_s_at	IDH3B; IDH3B; H-IDHB; MGC903; FLJ11043	AF023265	20p13	Hs.155410	1.167609	Down	0.0034737 11	1.1832137	Down	0.0038835	synonyms: H-IDHB, MGC903, FLJ11043; isocitric dehydrogenase; NAD+-specific isocitrate dehydrogenase beta precursor; NAD+-specific isocitrate dehydrogenase b subunit; NAD+-specific ICDH; isocitrate dehydrogenase, NAD(+)-specific, mitochondrial, beta subunit; Homo sapiens isocitrate dehydrogenase 3 (NAD+) beta (IDH3B), nuclear gene encoding mitochondrial protein, transcript variant 1, mRNA.
203946_s_at	ARG2	U75667	14q24.1-q24.3	Hs.172851	1.241001	Down	0.006993609	1.1794939	Down	0.0060619	kidney arginase; nonhepatic arginase; L-arginine amidinohydrolase; L-arginine ureahydrolase; A-II; Homo sapiens arginase, type II (ARG2), nuclear gene encoding mitochondrial protein, mRNA.
200880_at	DNAJA1	AL534104	9p13-p12	Hs.94	1.255564	Down	0.000175313	1.2076009	Down	5.252E-05	DnaJ (Hsp40) homolog, subfamily A, member 1
213921_at	SST; SST; SMST	NM_001048	3q28	Hs.12409	1.515051	Down	0.000215427	1.636124	Down	7.312E-05	synonym: SMST; Homo sapiens somatostatin (SST), mRNA.

210014_x_at	IDH3B; IDH3B; H-IDHB; MGC903; FLJ11043	AF023266	20p13	Hs.155410	1.122301	Down	0.019203283	1.121091	Down	0.01916	synonyms: H-IDHB, MGC903, FLJ11043; isocitric dehydrogenase; NAD+-specific isocitrate dehydrogenase beta precursor; NAD+-specific isocitrate dehydrogenase b subunit; NAD+-specific ICDH; isocitrate dehydrogenase, NAD(+)-specific, mitochondrial, beta subunit; Homo sapiens isocitrate dehydrogenase 3 (NAD+) beta (IDH3B), nuclear gene encoding mitochondrial protein, transcript variant 1, mRNA.
220045_at	NEUROD6; NEUROD6; Atoh2; NEX1M; Math-2	NM_022728		Hs.45152	1.267805	Down	0.008816781	1.3729298	Down	8.878E-03	synonyms: Atoh2, NEX1M, Math 2; Homo sapiens neurogenic differentiation 6 (NEUROD6), mRNA.
203336_s_at	ICAP-1A	AL548363	2p25.2	Hs.173274	1.316161	Down	0.000466987	1.3671769	Down	1.818E-05	integrin cytoplasmic domain-associated protein 1
218289_s_at	FLJ23251	NM_024818	3q22.1	Hs.170737	1.15484	Down	0.022580688	1.1592489	Down	0.0080202	Homo sapiens hypothetical protein FLJ23251 (FLJ23251), mRNA.
204679_at	KCNK1; KCNK1; DPK; HOHO; TWIK1; TWIK-1	NM_002245	1q42-q43	Hs.79351	1.263524	Down	0.000834684	1.2888284	Down	3.552E-05	synonyms: DPK, HOHO, TWIK1, TWIK-1; potassium inwardly-rectifying channel, subfamily K, member 1; potassium channel, subfamily K, member 1 (TWIK-1); Homo sapiens potassium channel, subfamily K, member 1 (KCNK1), mRNA.

202825_at	SLC25A4; SLC25A4; T1; ANT; ANT1; PEO2; PEO3	NM_001151	4q35	Hs.2043	1.243055	Down	0.003755193	1.1702655	Down	0.004136	synonyms: T1, ANT, ANT1, PEO2, PEO3; adenine nucleotide translocator 1 (skeletal muscle); Homo sapiens solute carrier family 25 (mitochondrial carrier; adenine nucleotide translocator), member 4 (SLC25A4), nuclear gene encoding mitochondrial protein, mRNA.
218674_at	FLJ13611	NM_024941	5q12.2	Hs.28285 8	1.280891	Down	3.93672E-05	1.1687894	Down	0.0110943	Homo sapiens hypothetical protein FLJ13611 (FLJ13611), mRNA.
218946_at	HIRIP5; HIRIP5; CGI-33	NM_015700	2p15-p13	Hs.43043 9	1.20213	Down	0.000950488	1.2521308	Down	8.482E-05	synonym: CGI-33; HIRIP5 protein; HIRA-interacting protein 5; Homo sapiens HIRA interacting protein 5 (HIRIP5), mRNA.
201597_at	COX7A2; COX7A2; COX7AL; COX7AL1; COXVIIa-L	NM_001865	6q12	Hs.70312	1.149256	Down	0.00795477	1.182428	Down	1.847E-05	synonyms: COX7AL, COX7AL1, COXVIIa-L; hepatic cytochrome-c oxidase chain VIIa; Homo sapiens cytochrome c oxidase subunit VIIa polypeptide 2 (liver) (COX7A2), nuclear gene encoding mitochondrial protein, mRNA.
203663_s_at	COX5A; COX5A; VA; COX-VA	NM_004255	15q25	Hs.32383 4	1.197943	Down	0.004379827	1.2294325	Down	7.346E-05	synonyms: VA, COX, COX-VA; cytochrome c oxidase polypeptide, mitochondrial precursor; Homo sapiens cytochrome c oxidase subunit Va (COX5A), nuclear gene encoding mitochondrial protein, mRNA.

206552_s_at	TAC1; TAC1; NK2; NKNA; TAC2	NM_003182	7q21-q22	Hs.2563	1.662809	Down	2.27281E-07	1.5689366	Down	2.145E-06	synonyms: NK2, NKNA, TAC2; neurokinin A; neurokinin alpha; tachykinin 2; substance K; neuropeptide K; neuropeptide gamma; substance P; neurokinin 1; neurokinin 2; neuromedin L; Homo sapiens tachykinin, precursor 1 (substance K, substance P, neurokinin 1, neurokinin 2, neuromedin L, neurokinin alpha, neuropeptide K, neuropeptide gamma) (TAC1), transcript variant beta, mRNA.; synonyms: NK2, NKNA, TAC2; neurokinin A; neurokinin alpha; tachykinin 2; substance K; neuropeptide K; neuropeptide gamma; substance P; neurokinin 1; neurokinin 2; neuromedin L; Homo sapiens tachykinin, precursor 1 (substance K, substance P, neurokinin 1, neurokinin 2, neuromedin L, neurokinin alpha, neuropeptide K, neuropeptide gamma) (TAC1), transcript variant alpha,
202233_s_at	UQCRH	NM_006004		Hs.73818	1.148508	Down	0.025106827	1.1682167	Down	3.697E-05	Homo sapiens ubiquinol-cytochrome c reductase hinge protein (UQCRH), mRNA.
218573_at	MAGEH1; MAGEH1; APR-1	NM_014061	Xp11.22	Hs.279319	1.167834	Down	0.018662092	1.2202881	Down	8.034E-05	synonym: APR-1; restin; MAGE-H1 antigen; Homo sapiens APR-1 protein (MAGEH1), mRNA.

217769_s_at	C13orf12; C13orf12; HSPC014; 25100480068Rik	NM_016532	13q12.13	Hs.27881 3	1.144417	Down	0.009883437	1.1719335	Down	6.667E-05			synonyms: HSPC014, 25100480068Rik; Homo sapiens chromosome 13 open reading frame 12 (C13orf12), mRNA.
201323_at	EBNA1BP2; EBNA1BP2; P40; EBP2; NOBP	NM_006824	1p35-p33	Hs.34586 8	1.13668	Down	0.018139154	1.1688038	Down	4.837E-05			synonyms: P40, EBP2, NOBP; cell proliferation-associated protein; nuclear protein p40; homolog of yeast EBNA1-binding protein; nuclear FGF3 binding protein; EBNA1-binding protein 2; Homo sapiens EBNA1 protein 2; Homo sapiens EBNA1 binding protein 2 (EBNA1BP2), mRNA.
219819_at	DIRAS2; DIRAS2; Di-Ras2; DKFZp761C071 21	NM_017594	9q22.1	Hs.18563 6	1.28122	Down	3.394735E-05	1.2324031	Down	1.628E-05			synonyms: Di-Ras2, DKFZp761C071121; member of the Ras family/small GTP-binding protein; Homo sapiens DIRAS family, GTP-binding RAS like 2 (DIRAS2), mRNA.
213924_at	MPPE1	BF476502	18p11.21	Hs.15414 5	1.19484	Down	0.004653387	1.1134946	Down	0.03622816			metallo phosphoesterase
218755_s_at	FBS1; FBS1; FLJ11618	NM_022452	16p11.2	Hs.77735	1.308398	Up	5.966966E-05	1.2807998	Up	4.124E-05			synonyms: FBS, FLJ11618; likely ortholog of mouse fibrosin; Homo sapiens fibrosin 1 (FBS1), mRNA.
202806_at	WFS1; WFS1; WFRS; DFNA6; DFNA14; DFNA38; DIDMOAD; WOLFRAMIN	NM_006005	4p16	Hs.26077	1.264488	Up	1.963TE-05	1.2121222	Up	0.0049794			synonyms: WFS, WFRS, DFNA6, DFNA14, DFNA38, DIDMOAD, WOLFRAMIN; Homo sapiens Wolfram syndrome 1 (wolframin) (WFS1), mRNA.
214203_s_at	PRODH	AA074145	22q11.21	Hs.34387 4	1.410089	Up	0.003560936	1.1914316	Up	0.0336675			proline dehydrogenase (oxidase) 1

204294_at	AMT; AMT; GCE; NKH; GCST	NM_000481	3p21.2-p21.1	Hs.102	1.20989	Up	0.003991535	1.0981119	Up	0.0102842	synonyms: GCE, NKH, GCST; Homo sapiens aminomethyltransferase (glycine cleavage system protein T) (AMT), mRNA.
209275_s_at	CLN3; CLN3; BTS	AF015593	16p12.1	Hs.194650	1.194657	Up	0.010213986	1.1260952	Up	0.0776445	synonym: BTS; Homo sapiens ceroid-lipofuscinosis, neuronal 3, juvenile (Batten, Spielmeyer-Vogt disease) (CLN3), mRNA.
209600_s_at	ACOX1; ACOX1; MGC1198; PALMCOX	S69189	17q24-17q25	Hs.378991	1.271368	Up	0.003383436	1.1690975	Up	0.0599128	synonyms: ACOX, PALMCOX, MGC1198; acyl-coenzyme A oxidase 1; Homo sapiens acyl-Coenzyme A oxidase 1, palmitoyl (ACOX1), transcript variant 1, mRNA.; synonyms: ACOX, PALMCOX, MGC1198; acyl-coenzyme A oxidase 1; Homo sapiens acyl-Coenzyme A oxidase 1, palmitoyl (ACOX1), transcript variant 2, mRNA.
202275_at	G6PD; G6PD; G6PD1	NM_000402	Xq28	Hs.80206	1.327344	Up	0.009288556	1.1621796	Up	0.0821313	synonym: G6PD1; Homo sapiens glucose-6-phosphate dehydrogenase (G6PD), nuclear gene encoding mitochondrial protein, mRNA.
208369_s_at	GCDH	NM_013976	19p13.2	Hs.184141	1.179371	Up	0.004779557	1.0740628	Up	0.0802165	Homo sapiens glutaryl-Coenzyme A dehydrogenase (GCDH), nuclear gene encoding mitochondrial protein, transcript variant 1, mRNA.; Homo sapiens glutaryl-Coenzyme A dehydrogenase (GCDH), nuclear gene encoding mitochondrial protein, transcript variant 2, mRNA.

213818_x_at	COL5A1	AI862325	11	Hs.381134	1.582872	Up	3.03281E-05	1.1283786	Up	0.20423431	ESTs, Moderately similar to RIKEN cDNA 1810059G22 [Mus musculus] [M.musculus]
214892_x_at	NY-REN-24	BC004282	19p13.3	Hs.128425	1.290886	Up	3.8958E-05	1.0386863	Up	0.43972711	NY-REN-24 antigen
215558_x_at	HMGCL; HMGCL; HL	AL031295	1p36.1-p35	Hs.831	1.283746	Up	3.92831E-05	1.0334089	Up	0.5203439	synonym: HL; 3-hydroxy-3-methylglutaryl-Coenzyme A lyase; 3-hydroxy-3-methylglutaryl-Coenzyme A lyase (hydroxymethylglutaricaciduria); Homo sapiens 3-hydroxymethyl-3-methylglutaryl-Coenzyme A lyase (hydroxymethylglutaricaciduria) (HMGCL), mRNA.
207506_at	TXNL2; TXNL2; PICOT	NM_006541	6p25.3	Hs.42644	1.376835	Up	0.005318749	1.0210061	Up	0.66528808	synonym: PICOT; PKC-interacting cousin of thioredoxin; Homo sapiens thioredoxin-like 2 (TXNL2), mRNA.
205236_x_at	SOD3	NM_003102	4p16.3-q21	Hs.2420	1.280517	Up	0.001685857	1.0086441	Up	0.88220476	Homo sapiens superoxide dismutase 3, extracellular (SOD3), mRNA.
203576_at	BCAT2; BCAT2; BCT2	NM_001190	19q13	Hs.101406	1.287101	Up	0.000421341	1.0767066	Up	0.19972382	synonym: BCT2; predicted mature protein begins at amino acid 28; Homo sapiens branched chain aminotransferase 2, mitochondrial (BCAT2), mRNA.
208581_x_at	MT1X	NM_005952	16q13	Hs.374950	1.547521	Up	0.010241902	1.3210147	Up	0.0043787	synonyms: MT1, MT-1l; Homo sapiens metallothionein 1X (MT1X), mRNA.

purine metabolism (matrix)

203722_at	ALDH4A1; ALDH4A1; P5CD; P5CDH; P5CDh; P5CDhL; P5CDhS	NM_003748	1_p36	H5.77448	1.432904 Up	0.021869834 1.1849056 Up	0.07248872 synonyms: P5CD, ALDH4, P5CDH, P5CDhL, P5CDhS; aldehyde dehydrogenase 4; mitochondrial delta-1-pyrroline 5-carboxylate dehydrogenase; P5C dehydrogenase; Homo sapiens aldehyde dehydrogenase 4 family, member A1 (ALDH4A1), nuclear gene encoding mitochondrial protein, transcript variant protein, transcript variant P5CDhL, mRNA.; synonyms: P5CD, ALDH4, P5CDH, P5CDhL, P5CDhS; aldehyde dehydrogenase 4; mitochondrial delta-1-pyrroline 5-carboxylate dehydrogenase; P5C dehydrogenase; Homo sapiens aldehyde dehydrogenase 4 family, member A1 (ALDH4A1), nuclear gene encoding mitochondrial protein, transcript variant P5CDhS, mRNA

	202148_s_at	PYCR1; PYCR1; P5C; P5CR; PP222	NM_006907	17q25.3	Hs.79217	1.12087	Up	0.121682507	1.1226109	Up	0.08014123	synonyms: P5C, P5CR, PYCR, PP222; P5C reductase; Homo sapiens pyrroline-5-carboxylate reductase 1 (PYCR1), nuclear gene encoding mitochondrial protein, transcript variant 1, mRNA.; synonyms: P5C, P5CR, PYCR, PP222; P5C reductase; Homo sapiens pyrroline-5-carboxylate reductase 1 (PYCR1), nuclear gene encoding mitochondrial protein, transcript variant 2, mRNA.
metallo proteins	208581_x_at	MT1X	NM_005952	16q13	Hs.374950	1.647621	Up	0.010241902	1.3210147	Up	0.0043787	synonyms: MT1, MT-1l; Homo sapiens metallothionein 1X (MT1X), mRNA.
	204326_x_at	MT1L	NM_002450	16q13	Hs.380778	1.623265	Up	0.017017261	1.232518	Up	0.0261237	synonyms: MT1, MT1R; metallothionein 1R; Homo sapiens metallothionein 1L (MT1L), mRNA.
	204745_x_at	MT1G; MT1G; MGC12386	NM_005950	16q13	Hs.433391	1.26869	Up	0.0322672	1.364678	Up	0.0359803	synonyms: MT1, MGC12386; Homo sapiens metallothionein 1G (MT1G), mRNA.
	206461_x_at	MT1H	NM_005951	16q13	Hs.2667	1.355566	Up	0.025686532	1.3155074	Up	0.0133935	synonym: MT1; Homo sapiens metallothionein 1H (MT1H), mRNA.
	211456_x_at		AF333388		Hs.367850	1.354488	Up	0.018339171	1.3387926	Up	0.0097775	MT-1H-like protein; mutant as compared to wild-type sequence MT-1H in GenBank Accession Number X64834; Homo sapiens metallothionein 1H-like protein mRNA, complete cds.

	212185_x_at	MT2A	NM_005953	16q13	Hs.116786	1.384172	Up	0.033875359	1.3559748	Up	0.0171696	synonym: MT2; This sequence comes from Fig. 2; Homo sapiens metallothionein 2A (MT2A), mRNA.
	212859_x_at	MT1E	BF217861	16q13	Hs.433205	1.34909	Up	0.012855859	1.2187557	Up	0.023793	metallothionein 1E (functional)
	217165_x_at	MT1F; MT1F; MGC32732	M10943	16q13		1.186389	Up	0.226324931	1.2547097	Up	0.0079279	synonyms: MT1, MGC32732; Homo sapiens metallothionein 1F (functional) (MT1F), mRNA.
	213629_x_at	MT1F	BF246115	16q13	Hs.381097	1.120311	Up	0.312657589	1.1835955	Up	0.057089	metallothionein 1F (functional)
Ornithine related	201599_at	OAT; OAT; HOGA	NM_000274	10q26	Hs.75485	1.210476	Down	0.003978229	0.8748633	Down	0.01912881	synonym: HOGA; Ornithine aminotransferase; Homo sapiens ornithine aminotransferase (gyrate atrophy) (OAT), nuclear gene encoding mitochondrial protein, mRNA.
	212461_at	OAZIN	BF793951	8q22.3	Hs.223014	1.239532	Down	0.016483367	1.1311716	Down	0.0150402	ornithine decarboxylase antizyme inhibitor
	201364_s_at	OAZ2	AF242521	15q22.1	Hs.74563	1.115702	Down	0.079601376	1.1385592	Down	0.0359062	protein translation dependent on +1 ribosomal frameshift; antizyme 2; Homo sapiens ornithine decarboxylase antizyme 2 (OAZ2), mRNA.
Arginine Related[d]	203946_s_at	ARG2	U75667	14q24.1-q24.3	Hs.172851	1.241001	Down	0.006993609	1.1794939	Down	0.0060619	kidney arginase; nonhepatic arginase; L-arginine amidinohydrolase; L-arginine ureahydrolase; A-II; Homo sapiens arginase, type II (ARG2), nuclear gene encoding mitochondrial protein, mRNA.

	202282_x_at	DDAH2; DDAH2; G6a; NG30; DDAHII	NM_013974	6p21.3	Hs.24738 2	1.218874 Up	0.045169089	1.1140322 Up	0.00574631	synonyms: G6a, NG30, DDAHII; dimethylarginine dimethylaminohydrolase II; Homo sapiens dimethylarginine dimethylaminohydrolase 2 (DDAH2), mRNA.
ATP synthase	201089_at	ATP6V1B2; ATP6V1B2; HO57; VATB; VPP3; Vma2; ATP8B2; ATP6B1B2	NM_001693	8p22-p21	Hs.1697	1.203827 Down	0.006759781	0.8220404 Down	0.00155735	synonyms: HO57, VATB, VPP3, Vma2, ATP8B2, ATP6B1B2; vacuolar proton pump B isoform 2; endomembrane proton pump 58 kDa subunit; vacuolar ATP synthase subunit B, brain isoform; V-ATPase B2 subunit; H(+)-transporting two-sector ATPase, 56/58kD subunit, isoform 2; Homo sapiens ATPase, H+ transporting, lysosomal 56/58kDa, V1 subunit B, isoform 2 (ATP6V1B2), mRNA.
(mitochondrial)										

201443_s_at	ATP6IP2; ATP6IP2; M8-9; APT6M8-8; ATP6M8-9	AF248986	Xq21	Hs.18343 4	1.1 38442 Down	0.019887088	0.68716057 Down	0.007722083	synonyms: M8-9, APT6M8-9, ATP6M8-8; ATPase, H+ transporting, lysosomal (vacuolar proton pump) membrane sector associated protein M8-9; vacuolar ATP synthase membrane sector associated protein M8-9; V-associated protein M8.9 subunit; ATPase ATPase M8.9 subunit; ATPase membrane sector associated protein M8-9; renin receptor; Homo sapiens ATPase, H+ transporting, lysosomal interacting protein 2 (ATP6IP2); mRNA.
201444_s_at	ATP6IP2; ATP6IP2; M8-9; APT6M8-8; ATP6M8-9	NM_005765	Xq21	Hs.18343 4	1.302733 Down	0.012483331	0.78791 t 1 Down	0.01120689	synonyms: M8-9, APT6M8-9, ATP6M8-8; ATPase, H+ transporting, lysosomal (vacuolar proton pump) membrane sector associated protein M8-9; vacuolar ATP synthase membrane sector associated protein M8-9; V-associated protein M8.9 subunit; ATPase ATPase M8.9 subunit; ATPase membrane sector associated protein M8-9; renin receptor; Homo sapiens ATPase, H+ transporting, lysosomal interacting protein 2 (ATP6IP2); mRNA.

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	202874_s_at	ATP6V1C1; ATP6V1C1; VATC; Vma5; ATP6C; ATP6D; FLJ20057	NM_001695	8q22.3	Hs.86905	1.244045	Down	0.012519633	0.8194812	Down	0.01590041	synonyms: VATC, Vma5, ATP6C, ATP6D, FLJ20057; vacuolar proton-ATPase, subunit C, VI domain; H+-transporting ATPase chain C, vacuolar; vacuolar proton pump C subunit; H(+)-transporting two-sector ATPase, subunit C; vacuolar ATP synthase subunit C; V-ATPase C subunit; vacuolar proton pump, 42-kD subunit; vat c; H+ -ATPase C subunit; ATPase, H+ transporting, lysosomal, 42kD; ATPase, H+ transporting, lysosomal, subunit C; Homo sapiens ATPase, H+ transporting, lysosomal 42kDa, V1 subunit C, isoform 1 (ATP6V1C1), mRNA.
ATP synthase	202325_s_at	ATP5J; ATP5J; ATPM; ATP5A	NM_001685	21q21.1	Hs.73851	1.198518	Down	0.00068097	0.8948735	Down	0.00601164	synonyms: ATP5, ATPM, ATP5A; ATP synthase, H+ transporting (ATPase, mitochondrial); ATP synthase coupling factor 6; Homo sapiens ATP synthase, H+ transporting, mitochondrial F0 complex, subunit F6 (ATP5J), nuclear gene encoding mitochondrial protein, mRNA.
(vacuolar)	207507_s_at	ATP5G3	NM_001689	2q31.1	Hs.429	1.193118	Down	0.005733489	0.8544746	Down	0.00014404	ATP synthase, mitochondrial, C subunit-3; Homo sapiens ATP synthase, H+ transporting, mitochondrial F0 complex, subunit c (subunit 9) isoform 3 (ATP5G3), mRNA.

207508_at	ATP5G3	NM_001689	2q31.1	Hs.429	1.131766	Down	0.034321	0.8851774	Down	0.00238781 ATP synthase, mitochondrial, C subunit-3; Homo sapiens ATP synthase, H+ transporting, mitochondrial F0 complex, subunit c (subunit 9) isoform 3 (ATP5G3), mRNA.
208745_at	ATP5L	AA917672	11q23	Hs.107476	1.187875	Down	0.011546587	0.8447284	Down	0.00101289 ATP synthase, H+ transporting, mitochondrial F0 complex, subunit g
208870_x_at	ATP5C1; ATP5C1; ATP5CL1	BC000931	10q22-q23	Hs.155433	1.124441	Down	0.019343048	0.9124323	Down	0.01392037 synonyms: ATP5C, ATP5CL1; H(heart)-type ATP synthase gamma-subunit; ATP synthase, H+ transporting, mitochondrial F1 complex, gamma polypeptide-like 1; Homo sapiens ATP synthase, H+ transporting, mitochondrial F1 complex, gamma polypeptide 1 (ATP5C1), mRNA.
211755_s_at	ATP5F1	BC005960	1p13.1	Hs.81634	1.162583	Down	0.003380778	0.8787883	Down	0.00153431 ATP synthase, H+ transporting, mitochondrial F0 complex, subunit b, isoform 1
213738_s_at	ATP5A1	AI587323	18q12-q21	Hs.405985	1.144936	Down	0.009591663	0.8780464	Down	0.00385739 ATP synthase, H+ transporting, mitochondrial F1 complex, alpha subunit, isoform 1, cardiac muscle

Complex 1

201304_at	NDUFA5; NDUFA5; B13; NUFM; UQOR13; FLJ12147; CI-13KD-B	NM_005000	7q32	Hs.83916	1.25	1252	Down	0.004319206	0.8638455	Down	0.01864249 synonyms: B13, NUFM, UQOR13, FLJ12147, CI-13KD-B; NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 5 (13kD, B13); Complex I-13KD-B; ubiquinone reductase; type I dehydrogenase; Homo sapiens NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 5, 13kDa (NDUFA5), nuclear gene encoding mitochondrial protein, mRNA.
202001_s_at	NDUFA6; NDUFA6; B14	NM_002490	22q13.2-q13.31	Hs.27441 6	1.1	80887	Down	0.002838277	0.8384088	Down	0.00056884 synonym: B14; NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 6; NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 6 (14kD, B14); Homo sapiens NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 6, 14kDa (NDUFA6), mRNA.
202077_at	NDUFAB1; NDUFAB1; SDAP	NM_005003		Hs.5556	1.17	8996	Down	0.001418435	0.8560824	Down	0.00023024 synonym: SDAP; NDUFAB1 subunit; NADH dehydrogenase (ubiquinone) 1, alpha/beta subcomplex, 1 (8kD, SDAP); Homo sapiens NADH dehydrogenase (ubiquinone) 1, alpha/beta subcomplex, 1, 8kDa (NDUFAB1), mRNA.

203371_s_at	NDUFB3; NDUFB3; B12	NM_002491	2q31.3	Hs.109760	1.193323	Down	0.007489942	0.83959 Down	0.00103955	synonym: B12; NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 3 (12kD, B12); Homo sapiens NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 3, 12kDa (NDUFB3), mRNA.
203613_s_at	NDUFB6; NDUFB6; B17	NM_002493		Hs.109646	1.138507	Down	0.022389242	0.8259696 Down	0.00038684	synonym: B17; NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 6 (17kD, B17); Homo sapiens NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 6, 17kDa (NDUFB6), mRNA.
203621_at	NDUFB5; NDUFB5; SGDH	NM_002492	3q27.1	Hs.19236	1.151684	Down	0.042430348	0.8951788 Down	0.01913304	synonym: SGDH; NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5 (16kD, SGDH); Homo sapiens NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 16kDa (NDUFB5), mRNA.
206790_s_at	NDUFB1; NDUFB1; MNLL; CI-SGDH	NM_004545	14q32.12	Hs.183435	1.190237	Down	0.004989016	0.8718049 Down	0.00309552	synonyms: MNLL, CI-SGDH; NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 1 (7kD, MNLL); Homo sapiens NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 1, 7kDa (NDUFB1), mRNA.

209303_at	NDUFS4; NDUFS4; AQDQ	BC003270	5q11.1	Hs.10758	1.15407 Down	0.023114134	0.833423 Down	0.00048245	synonym: AQDQ; NADH dehydrogenase (ubiquinone) Fe-S protein 4 (18kD) (NADH-coenzyme Q reductase); NADH dehydrogenase (ubiquinone) Fe-S protein 4, 18kD (NADH-coenzyme Q; mitochondrial respiratory chain complex I (18-KD subunit); Homo sapiens NADH dehydrogenase (ubiquinone) Fe-S protein 4, 18kDa (NADH-coenzyme Q reductase) (NDUFS4), mRNA.
217773_s_at	NDUFB4; NDUFB4; MLRQ	NM_002489		Hs.50098	1.135565 Down	0.005342988	0.869414 Down	0.00144186	synonym: MLRQ; NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4 (9kD, MLRQ); Homo sapiens NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9kDa (NDUFA4), mRNA.
218181_s_at	NDUFC2; NDUFC2; B14.5b	NM_004549		Hs.19331 3	1.129474 Down	0.031751159	0.8886449 Down	0.00161606	synonym: B14.5b; NADH dehydrogenase (ubiquinone) 1, subcomplex unknown, 2 (14.5kD, B14.5b); Homo sapiens NADH dehydrogenase (ubiquinone) 1, subcomplex unknown, 2, 14.5kDa (NDUFC2), mRNA.
218226_s_at	NDUFB4; NDUFB4; B15	NM_004547	3q13.33	Hs.22775 0	1.118038 Down	0.016901189	0.9283017 Down	0.03138745	synonym: B15; NDUFB4 subunit; NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4 (15kD, B15); Homo sapiens NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15kDa (NDUFB4), mRNA.

Complex 3

	202233_s_at	UQCRH	NM_006004		Hs.73818	1.148508	Down	0.025106508	0.8660056	Down	3.687E-05	Homo sapiens ubiquinol-cytochrome c reductase hinge protein (UQCRH), mRNA.
	208909_at	UQCRFS1; UQCRFS1; RIS1	BC000649	19q12-q13.1	Hs.3712	1.168573	Down	0.012592784	0.8257155	Down	0.0002244	synonym: RIS1; Homo sapiens ubiquinol-cytochrome c reductase, Rieske iron-sulfur polypeptide 1 (UQCRFS1), nuclear gene encoding mitochondrial protein, mRNA.
	200883_at	UQCRC2	NM_003366	16p12	Hs.173554	1.213288	Down	0.00595247	0.6653051	Down	0.01887364	Homo sapiens ubiquinol-cytochrome c reductase core protein II (UQCRC2), mRNA.
	205849_s_at	UQCRB; UQCRB; QPC; QP-C; UQBC; UQBP; UQPC	NM_006294	8q22	Hs.131255	1.185495	Down	0.012369038	0.8808683	Down	0.0017732	synonyms: QPC, QP-C, UQBC, UQBP, UQPC; Homo sapiens ubiquinol-cytochrome c reductase binding protein (UQCRB), mRNA.
	212600_s_at	UQCRC2	AV727381	16p12	Hs.173554	1.116486	Down	0.039363536	0.8932586	Down	0.00798423	ubiquinol-cytochrome c reductase core protein II
Complex 4	201597_at	COX7A2; COX7A2; COX7AL; COX7AL1; COXVIIa-L	NM_001865	6q12	Hs.70312	1.149356	Down	0.007984788	0.8457178	Down	1.847E-08	synonyms: COX7AL, COX7AL1, COXVIIa-L; hepatic cytochrome-c oxidase chain VIIa; Homo sapiens cytochrome c oxidase subunit VIIa polypeptide 2 (liver) (COX7A2), nuclear gene encoding mitochondrial protein, mRNA.
	202110_at	COX7B	NM_001866	Xq13.2	Hs.432170	1.130844	Down	0.045735159	0.8528508	Down	0.00061257	cytochrome-c oxidase chain VIIb; Homo sapiens cytochrome c oxidase subunit VIIb (COX7B), nuclear gene encoding mitochondrial protein, mRNA.

	203663_s_at	COX5A; COX6A; VA; COX-VA	NM_004255	15q25	Hs.32383 4	1.197943	Down	0.004378832	0.8135894	Down	7.2492E-06	synonyms: VA, COX, COX-VA; cytochrome c oxidase polypeptide, mitochondrial precursor; Homo sapiens cytochrome c oxidase subunit Va (COX5A), nuclear gene encoding mitochondrial protein, mRNA.
	203880_at	COX17	NM_005694		Hs.16297	1.199099	Down	0.014912612	0.8134965	Down	0.00016529	human homolog of yeast mitochondrial copper recruitment gene; COX17 (yeast) homolog, cytochrome c oxidase assembly protein; Homo sapiens COX17 homolog, cytochrome c oxidase assembly protein (yeast) (COX17), nuclear gene encoding mitochondrial protein, mRNA.
	214277_at	COX11	AI376724	17q22	Hs.24151 5	1.287888	Down	0.009150553	0.8805178	Down	0.02884133	COX11 homolog, cytochrome c oxidase assembly protein (yeast)
	217491_x_at	COX7CP1	AF042165	13q14-q21		1.148912	Down	0.031232864	0.9439594	Down	0.04448098	cytochrome c oxidase subunit VIIc; E.C. number =1.9.3.1; Homo sapiens cytochrome c oxidase subunit VIIc (COX7CP1) pseudogene, complete sequence.
	217329_x_at	COX7BP1; bK71497.1	AF042164	22q13		1.228784	Down	0.002837439	1.1261074	Down	0.08248038	cytochrome c oxidase subunit VIIb; E.C. number =1.9.3.1; Homo sapiens cytochrome c oxidase subunit VIIb (COX7BP1) pseudogene, complete sequence.
Holocytochrome c Synthetase	203746_at	HCCS	AI801013	Xp22.3	Hs.21157 1	1.168718	Down	0.002771726	0.8395424	Down	0.00835825	holocytochrome c synthase (cytochrome c heme-lyase)

	203746_s_at	HCCS; HCCS; CCHL	NM_005333	Xp22.3	Hs.211571	1.192373 Down	0.005742037	0.8000834 Down	0.01829721 synonym: CCHL; putative; Homo sapiens holocytochrome c synthase (cytochrome c heme-lyase) (HCCS), mRNA.
Adenine translocators	202825_at	SLC25A4; SLC25A4; T1; ANT; ANT1; PEO2; PEO3	NM_001151	4q35	Hs.2043	1.243055 Down	0.003755192	0.8646047 Down	0.00413595 synonyms: T1, ANT, ANT1, PEO2, PEO3; adenine nucleotide translocator 1 (skeletal muscle); Homo sapiens solute carrier family 25 (mitochondrial carrier; adenine nucleotide translocator), member 4 (SLC25A4), nuclear gene encoding mitochondrial protein, mRNA.
Glycine/Serine metabolism	204294_at	AMT; AMT; GCE; NKH; GCST	NM_000481	3p21.2-p21.1	Hs.102	1.26989 Up	0.003991538	1.0981119 Up	0.01028424 synonyms: GCE, NKH, GCST; Homo sapiens aminomethyltransferase (glycine cleavage system protein T) (AMT), mRNA.
Voltage dependant anion channels (in mitochondrial outer membrane)	211662_s_at	VDAC2	L08666	10q22	Hs.78902	1.12617 Down	0.014133989	0.8898027 Down	0.00348893 Homo sapiens voltage-dependent anion channel 2 (VDAC2), mRNA.
	217140_s_at	VDAC1P	AJ002428	Xq21-q22		1.215466 Down	0.016102094	0.7707105 Down	0.0008464 Homo sapiens VDAC1 pseudogene.
	208846_s_at	VDAC3; VDAC3; HD-VDAC3	U90943	8p11.2	Hs.7381	1.160087 Down	0.060742358	1.1200838 Down	0.0287343 synonym: HD-VDAC3; similar to mouse VDAC 3; Homo sapiens voltage-dependent anion channel 3 (VDAC3), mRNA.

Lactate metabolism	213564_x_at	LDHB	BE042354	12p12.2-p12.1	Hs.23448	1.104586 Down	0.030076871	0.9133205 Down	0.00138614	lactate dehydrogenase B	
	200650_s_at	LDHA; LDHA; LDH1	NM_005566	11p15.4	Hs.2795	1.134991 Down	0.03774599	1.1884595 Down	0.000774	synonym: LDH1; Homo sapiens lactate dehydrogenase A (LDHA), mRNA.	
	201030_x_at	LDHB	NM_002300	12p12.2-p12.1	Hs.23448	1.08367 Down	0.05927145	1.1007107 Down	0.0010265	Homo sapiens lactate dehydrogenase B (LDHB), mRNA.	
Isocitrate dehydrogenase	210014_s_at	IDH3B; IDH3B; H-IDHB; MGC903; FLJ11043	AF023268	20q13	Hs.15541	1.122301 Down	0.019203205	0.8519882 Down	0.0016005	synonym: H-IDHB; MGC903; FLJ11043; isocitric dehydrogenase; NAD+-specific isocitrate dehydrogenase beta precursor; NAD+-specific isocitrate dehydrogenase b subunit; NAD+-specific ICDH; isocitrate dehydrogenase, NAD(+)-specific, mitochondrial, beta subunit; Homo sapiens isocitrate dehydrogenase 3 (NAD+) beta (IDH3B), nuclear gene encoding mitochondrial protein, transcript variant 1, mRNA.	

210418_s_at	IDH3B; IDH3B; H-IDHB; MGC903; FLJ11043	AF023265	20p13	Hs.155410	1.157609	Down	0.009473713	0.8451559	Down	0.00368349	synonyms: H-IDHB, MGC903, FLJ11043; isocitric dehydrogenase; NAD+-specific isocitrate dehydrogenase beta precursor; NAD+-specific isocitrate dehydrogenase b subunit; NAD+-specific ICDH; isocitrate dehydrogenase, NAD(+)-specific, mitochondrial, beta subunit; Homo sapiens isocitrate dehydrogenase 3 (NAD+) beta (IDH3B), nuclear gene encoding mitochondrial protein, transcript variant 1, mRNA.
202069_s_at	IDH3A	AI826060	15q25.1-q25.2	Hs.250616	1.42986	Down	0.000593139	0.7369903	Down	0.00167327	isocitrate dehydrogenase 3 (NAD+) alpha
202070_s_at	IDH3A	NM_005530	15q25.1-q25.2	Hs.250616	1.107756	Down	0.098643023	1.1153047	Down	0.0234165	isocitrate dehydrogenase [NAD] subunit alpha, mitochondrial; NAD+-specific ICDH; NAD(H)-specific isocitrate dehydrogenase alpha subunit precursor; isocitrate dehydrogenase (NAD+) alpha chain precursor; H-IDH alpha; isocitric dehydrogenase; Homo sapiens isocitrate dehydrogenase 3 (NAD+) alpha (IDH3A), nuclear gene encoding mitochondrial protein, mRNA.

HMG related

	215569_x_at	HMGCL; HMGCL; HL	AL031295	1p36.1-p35	Hs.831	1.283746 Up	3.92631E-05			synonym: HL; 3-hydroxy-3-methylglutaryl-Coenzyme A lyase; 3-hydroxy-3-methylglutaryl-Coenzyme A lyase (hydroxymethylglutaricaciduria); Homo sapiens 3-hydroxymethyl-3-methylglutaryl-Coenzyme A lyase (hydroxymethylglutaricaciduria) (HMGCL), mRNA.
	202540_s_at	HMGCR	NM_000859	5q13.3-q14	Hs.11899	1.237843 Down	0.004508094	0.8558928 Down	0.02049312	Homo sapiens 3-hydroxy-3-methylglutaryl-Coenzyme A reductase (HMGCR), mRNA.
Glutamate metabolism	219933_at	GLRX2; GLRX2; GRX2	NM_016066	1q31.2-q31.3	Hs.5054	1.214851 Down	0.000650749	0.8082814 Down	0.0001692	synonym: GRX2; thioltransferase; contains nuclear membrane localization; CGI-133 protein; Homo sapiens glutaredoxin 2 (GLRX2), mRNA.
Oxidorelated	202017_at	EPHX1; EPHX1; MEH; EPOX	NM_000120	1q42.1	Hs.89649	1.406022 Up	0.065587794	1.4155563 Up	0.0222559	synonyms: MEH, EPHX, EPOX; Epoxide hydroxylase 1, microsomal (xenobiotic); Homo sapiens epoxide hydrolase 1, microsomal (xenobiotic) (EPHX1), mRNA.

Claims

1. Use of any of the following proteins in a screening assay to identify a potential therapeutic agent for the prevention, treatment, or amelioration of schizophrenia:
(i) proteins encoded by the following genes: PARG;OLR1; ARPC3; ARPC3; DNCLI1; PPM1A; ATPIF1; TIMM17A; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; FLJ13611; HIRIP5; TAC1; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1; OAT; OAZIN; OAZ2; ARG2; ATP6V1B2; ATP6IP2; ATP6V1C1; ATP5J; ATP5G3; ATP5L; ATP5C1; ATP5F1; ATP5A1; NDUFA5; NDUFA6; NDUFAB1; NDUFB3; NDUFB6; NDUFB5; NDUFB1; NDUFS4; NDUFA4; NDUFC2; NDUFB4; UQCRH; UQCRFS1; UQCRC2; UQCRB; UQCRC2; COX7A2; COX7B; COX5A; COX17; COX11; COX7CP1; COX7BP1; HCCS; SLC25A4; VDAC2; VDAC1P; VDAC3; LDHB; LDHA; IDH3B; IDH3A; HMGCR; GLRX2; FBS1; WFS1; PRODH; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-REN-24; TXNL2; SOD3; BCAT2; ALDH4A1; PYCR1; MT1X; MT1L; MT1G; MT1H; MT2A; MT1E; MT1F; DDAH2; AMT; HMGCL; EPHX1; or ii) nucleic acid encoding any of the proteins of (i) above.

2. Use of a regulator of expression of any of (i) of claim 1, in a screening assay to identify a potential therapeutic agent for the prevention, treatment, or amelioration of schizophrenia.

3. Use of a binding partner of any of (i) of claim 1 in a screening assay to identify a potential therapeutic agent for the prevention, treatment, or amelioration of schizophrenia.

4. Use of an expression vector comprising nucleic acid encoding any of (i) of claim 1 in a screening assay to identify a potential therapeutic agent for the prevention, treatment, or amelioration of schizophrenia.

5. Use of a cell or cell line expressing nucleic acid encoding any of (i) of claim 1 in a screening assay to identify a potential therapeutic agent for the prevention, treatment, or amelioration of schizophrenia.

6. Use according to claim 5, wherein the cell is a neural cell.

7. Use according to claim 5, wherein the cell is an oligodendrocyte.

8. A recombinant mouse in which expression of a gene encoding any of (i) of claim 1 is altered compared with expression of the corresponding gene in normal mice.

9. A recombinant mouse according to claim 8 in which expression of two or more of the genes is altered.

10. A recombinant mouse according to claim 8 or 9 which is a knockout mouse for the gene or genes.

11. Use of a recombinant mouse according to any of claims 8 to 10 as an animal model for schizophrenia.

12. Use of a mouse according to any of claims 8 to 10, or cells obtained or derived from the mouse, in a screening assay to identify a potential therapeutic agent for the prevention, treatment, or amelioration of schizophrenia.

13. A screening assay to identify a potential schizophrenia therapeutic agent for the prevention, treatment, or amelioration of schizophrenia which comprises screening for a modulator of expression of a gene encoding any of the proteins of (i) of claim 1 by: providing a system capable of expressing a gene encoding any of the proteins of (i) of claim 1; maintaining the system under conditions for expression of the gene in the presence and absence of a candidate modulator of expression of the gene; and determining the expression level of the gene in the presence and absence of the candidate modulator.

14. A screening assay according to claim 13, which comprises screening for an upregulator of expression of any of the following:

PARG;OLR1; ARPC3; ARPC3; DNCLI1; PPM1A; ATPIF1; TIMM17A; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; FLJ13611; HIRIP5; TAC1; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1; OAT; OAZIN; OAZ2; ARG2; ATP6V1B2; ATP6IP2; ATP6V1C1; ATP5J; ATP5G3; ATP5L; ATP5C1; ATP5F1; ATP5A1; NDUFA5; NDUFA6; NDUFAB1; NDUFB3; NDUFB6; NDUFB5; NDUFB1; NDUFS4; NDUFA4; NDUFC2; NDUFB4; UQCRH; UQCRFS1; UQCRC2; UQCRB; UQCRC2; COX7A2; COX7B; COX5A; COX17; COX11; COX7CP1; COX7BP1; HCCS; SLC25A4; VDAC2; VDAC1P; VDAC3; LDHB; LDHA; IDH3B; IDH3A; HMGCR; GLRX2.

15. A screening assay according to claim 13, which comprises screening for a downregulator of expression of any of the following:
FBS1; WFS1; PRODH; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-REN-24; TXNL2; SOD3; BCAT2; ALDH4A1; PYCR1; MT1X; MT1L; MT1G; MT1H; MT2A; MT1E; MT1F; DDAH2; AMT; HMGCL; EPHX1.

16. A screening assay to identify a potential schizophrenia therapeutic agent for the prevention, treatment, or amelioration of schizophrenia which comprises screening for a regulator of the activity of any of the proteins of (i) of claim 1 by: contacting the protein with a candidate regulator and determining the activity of the protein in the presence and absence of the candidate regulator.

17. A screening assay according to claim 16, which comprises screening for an enhancer or activator of the activity of any of the following proteins:
PARG;OLR1; ARPC3; ARPC3; DNCLI1; PPM1A; ATPIF1; TIMM17A; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; FLJ13611; HIRIP5; TAC1; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1; OAT; OAZIN; OAZ2; ARG2; ATP6V1B2; ATP6IP2; ATP6V1C1; ATP5J; ATP5G3; ATP5L; ATP5C1; ATP5F1; ATP5A1; NDUFA5; NDUFA6; NDUFAB1; NDUFB3; NDUFB6; NDUFB5; NDUFB1; NDUFS4; NDUFA4; NDUFC2; NDUFB4; UQCRH; UQCRFS1; UQCRC2; UQCRB; UQCRC2; COX7A2; COX7B; COX5A; COX17; COX11; COX7CP1; COX7BP1; HCCS; SLC25A4; VDAC2; VDAC1P; VDAC3; LDHB; LDHA; IDH3B; IDH3A; HMGCR; GLRX2.

18. A screening assay according to claim 16, which comprises screening for an inhibitor of the activity of any of the following proteins:
FBS1; WFS1; PRODH; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-REN-24; TXNL2; SOD3; BCAT2; ALDH4A1; PYCR1; MT1X; MT1L; MT1G; MT1H; MT2A; MT1E; MT1F; DDAH2; AMT; HMGCL; EPHX1.

19. A screening assay to identify a potential schizophrenia therapeutic agent for the prevention, treatment, or amelioration of schizophrenia which comprises screening for a regulator of the interaction of any of the proteins of (i) of claim 1 with a binding partner required for the biological effect of the protein by: contacting the protein with the binding partner in the presence of a candidate regulator, and determining binding of the protein to its binding partner in the presence and absence of the candidate regulator.

20. A screening assay according to claim 19, which comprises screening for an enhancer of the interaction of any of the following proteins with a binding partner required for the biological effect of the protein:
PARG;OLR1; ARPC3; ARPC3; DNCLI1; PPM1A; ATPIF1; TIMM17A; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; FLJ13611; HIRIP5; TAC1; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1; OAT; OAZIN; OAZ2; ARG2; ATP6V1B2; ATP6IP2; ATP6V1C1; ATP5J; ATP5G3; ATP5L; ATP5C1; ATP5F1; ATP5A1; NDUFA5; NDUFA6; NDUFAB1; NDUFB3; NDUFB6; NDUFB5; NDUFB1; NDUFS4; NDUFA4; NDUFC2; NDUFB4; UQCRH; UQCRFS1; UQCRC2; UQCRB; UQCRC2; COX7A2; COX7B; COX5A; COX17; COX11; COX7CP1; COX7BP1; HCCS; SLC25A4; VDAC2; VDAC1P; VDAC3; LDHB; LDHA; IDH3B; IDH3A; HMGCR; GLRX2.

21. A screening assay according to claim 19, which comprises screening for an inhibitor of the interaction of any of the following proteins with a binding partner required for the biological effect of the protein:

FBS1; WFS1; PRODH; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-REN-24; TXNL2; SOD3; BCAT2; ALDH4A1; PYCR1; MT1X; MT1L; MT1G; MT1H; MT2A; MT1E; MT1F; DDAH2; AMT; HMGCL; EPHX1.

22. A screening assay to identify a potential schizophrenia therapeutic agent for the prevention, treatment, or amelioration of schizophrenia which comprises screening for a binding partner of any of the proteins of (i) of claim 1 by: contacting the protein with a sample comprising a candidate binding partner, and determining whether the candidate binding partner binds to the protein.

23. A method of diagnosing whether a subject has, or is at risk of developing schizophrenia, which comprises determining the level of any of the proteins of (i) of claim 1, or the expression level of a gene encoding any of the proteins of (i) of claim 1, in a biological sample obtained from the subject, or in a sample derived from a biological sample obtained from the subject.

24. A method according to claim 23, wherein the biological sample comprises a peripheral tissue or cell type in which the level of the protein, or the expression level of the gene, correlates with the level of the corresponding protein, or the expression level of the corresponding protein, in the prefrontal cortex.

25. A method according to claim 24, wherein the peripheral tissue or cell type comprises a blood cell.

26. A method according to claim 25, wherein the blood cell is a macrophage, a monocyte, a lymphocyte, an erythrocyte, a platelet, a leukocyte (either a neutrophil, an eosinophil, or a basophil; a lymphocyte, or a monocyte).

27. A method of prevention, treatment, or amelioration of schizophrenia which comprises increasing the level or activity of any of the following proteins in the brain (in particular the prefrontal cortex) of a subject in need of such prevention, treatment, or amelioration:

PARG;OLR1; ARPC3; ARPC3; DNCLI1; PPM1A; ATPIF1; TIMM17A; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; FLJ13611; HIRIP5; TAC1; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1; OAT; OAZIN; OAZ2; ARG2; ATP6V1B2; ATP6IP2; ATP6V1C1; ATP5J; ATP5G3; ATP5L; ATP5C1; ATP5F1; ATP5A1; NDUFA5; NDUFA6; NDUFAB1; NDUFB3; NDUFB6; NDUFB5; NDUFB1; NDUFS4; NDUFA4; NDUFC2; NDUFB4; UQCRH; UQCRFS1; UQCRC2; UQCRB; UQCRC2; COX7A2; COX7B; COX5A; COX17; COX11; COX7CP1; COX7BP1; HCCS; SLC25A4; VDAC2; VDAC1P; VDAC3; LDHB; LDHA; IDH3B; IDH3A; HMGCR; GLRX2.

28. A method of prevention, treatment, or amelioration of schizophrenia which comprises reducing the level or activity of any of the following proteins in the brain (in particular the prefrontal cortex) of a subject in need of such prevention, treatment, or amelioration:

FBS1; WFS1; PRODH; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-REN-24; TXNL2; SOD3; BCAT2; ALDH4A1; PYCR1; MT1X; MT1L; MT1G; MT1H; MT2A; MT1E; MT1F; DDAH2; AMT; HMGCL; EPHX1.

Mitochondrial Changes

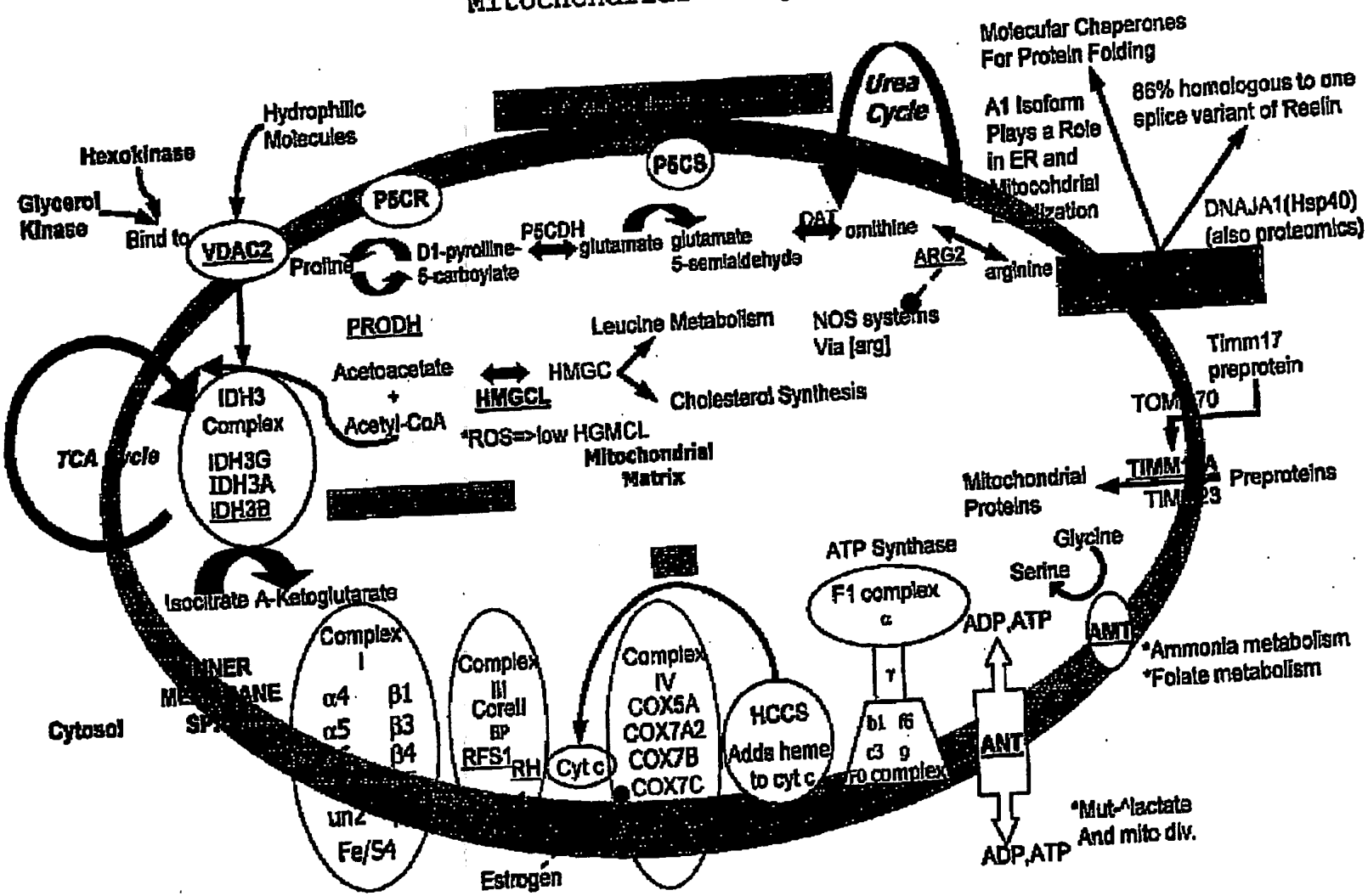

Figure 1

Figure 2

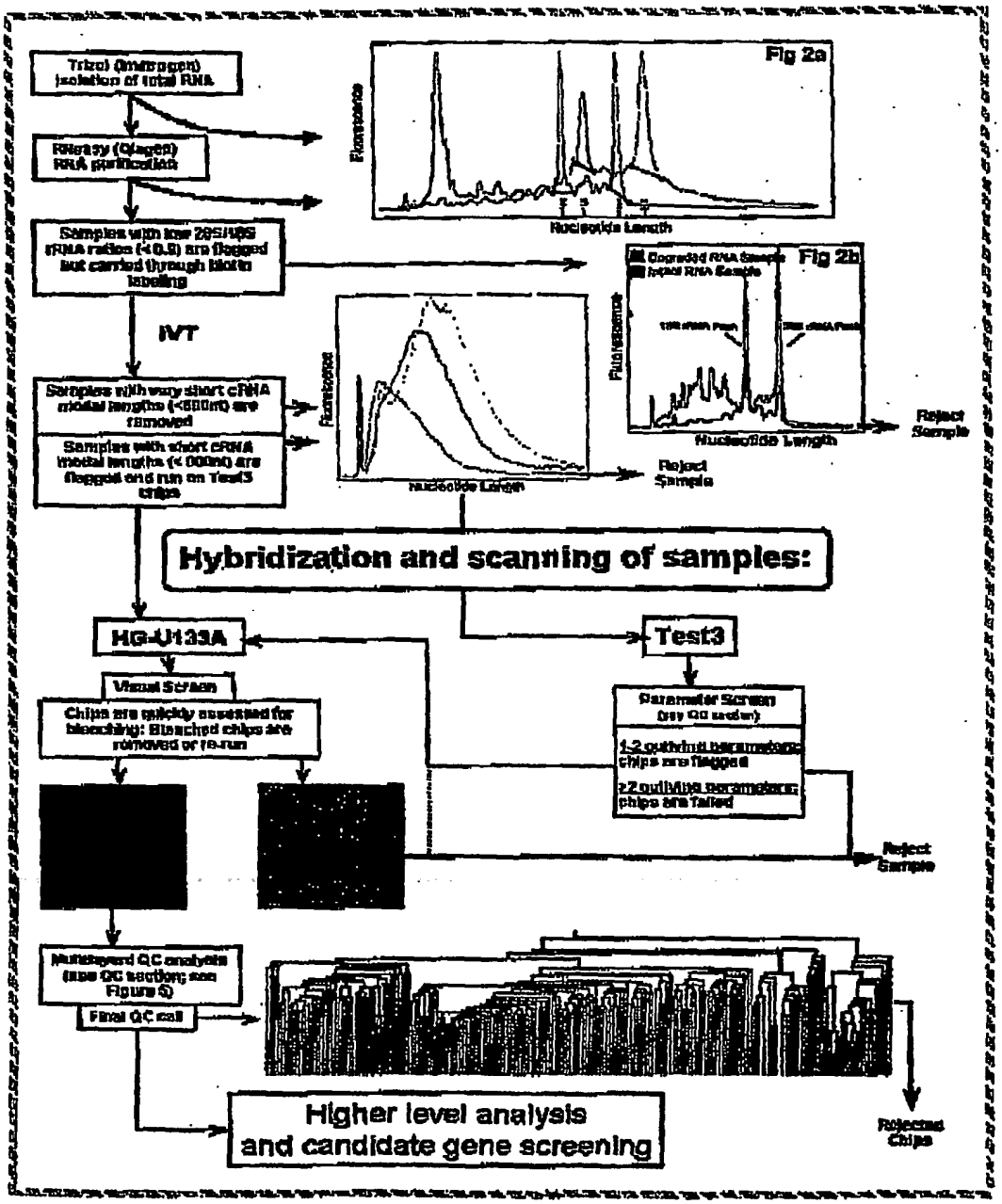
Trizol (Invitrogen) isolation of total RNA
RNeasy (Qiagen) RNA purification
Samples with low 28S/18S rRNA ratios (<0.5) are flagged but carried through biotin labeling
IVT
Samples with very short cRNA modal lengths (<600nt) are removed
Samples with short cRNA modal lengths (< 000nt) are flagged and run on Test3 chips
Fig 2a
Fluorescence
Nucleotide Length
Fig 2b
Degraded RNA Sample
Intact RNA Sample
Fluorescence
Nucleotide Length
Reject Sample
Reject Sample
Hybridization and scanning of samples:
HG-U133A
Visual Screen
Chips are quickly assessed for bleaching: Bleached chips are removed or re-run
Test3
Parameter Screen
1-2 outlying parameters: chips are flagged
>2 outlying parameters: chips are failed
Reject Sample
Multilayered QC analysis (see QC section; see Figure 5)
Final QC call
Higher level analysis and candidate gene screening
Rejected Chips

Figure 3

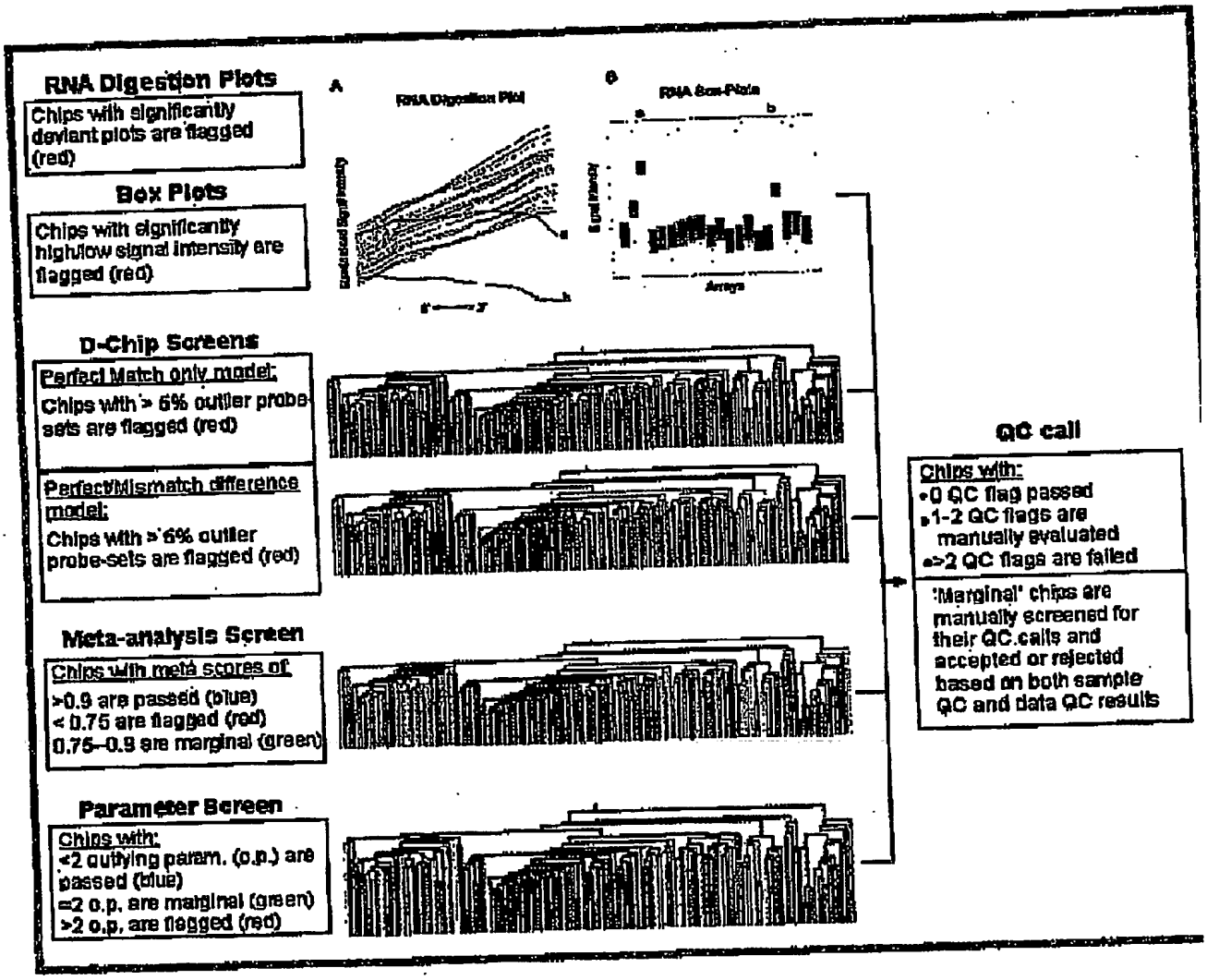
RNA Digestion Plots
Chips with significantly deviant plots are flagged (red)
Box Plots
Chips with significantly high/low signal intensity are flagged (red)
D-Chip Screens
Perfect Match only model:
Chips with > 6% outlier probe sets are flagged (red)
Perfect/Mismatch difference model:
Chips with > 6% outlier probe-sets are flagged (red)
Meta-analysis Screen
Chips with meta scores of
>0.9 are passed (blue)
< 0.75 are flagged (red)
0.75–0.9 are marginal (green)
Parameter Screen
Chips with:
<2 outlying param. (o.p.) are passed (blue)
=2 o.p. are marginal (green)
>2 o.p. are flagged (red)
A
RNA Digestion Plot
B
RNA Box-Plots
Arrays
QC call
Chips with:
•0 QC flag passed
•1-2 QC flags are manually evaluated
•=>2 QC flags are failed
'Marginal' chips are manually screened for their QC calls and accepted or rejected based on both sample QC and data QC results

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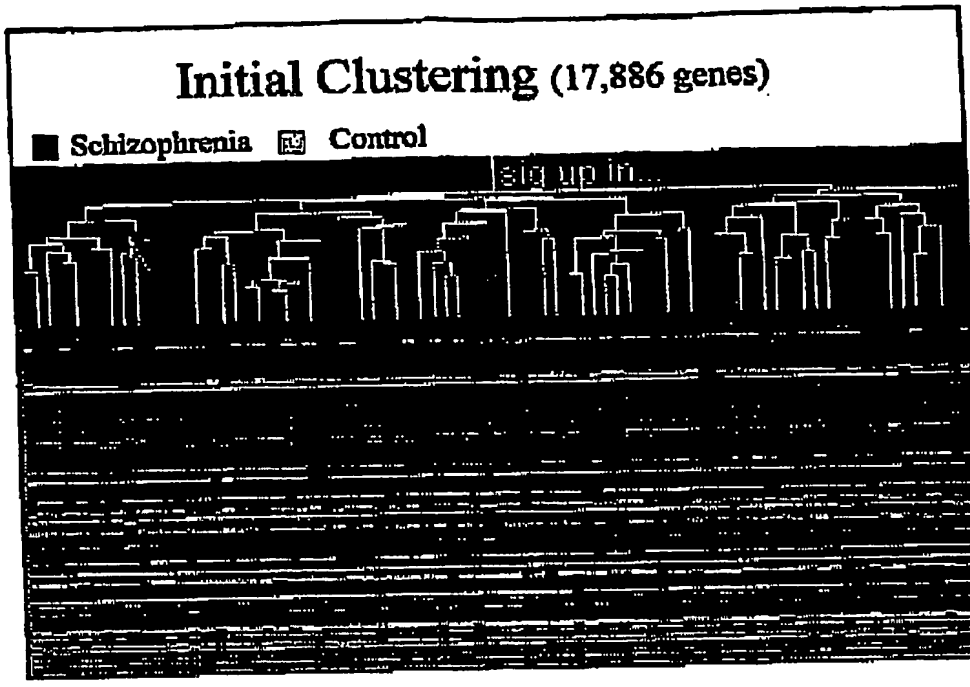
Figure 4


Initial Clustering (17,886 genes)
Schizophrenia
Control
sig up in...

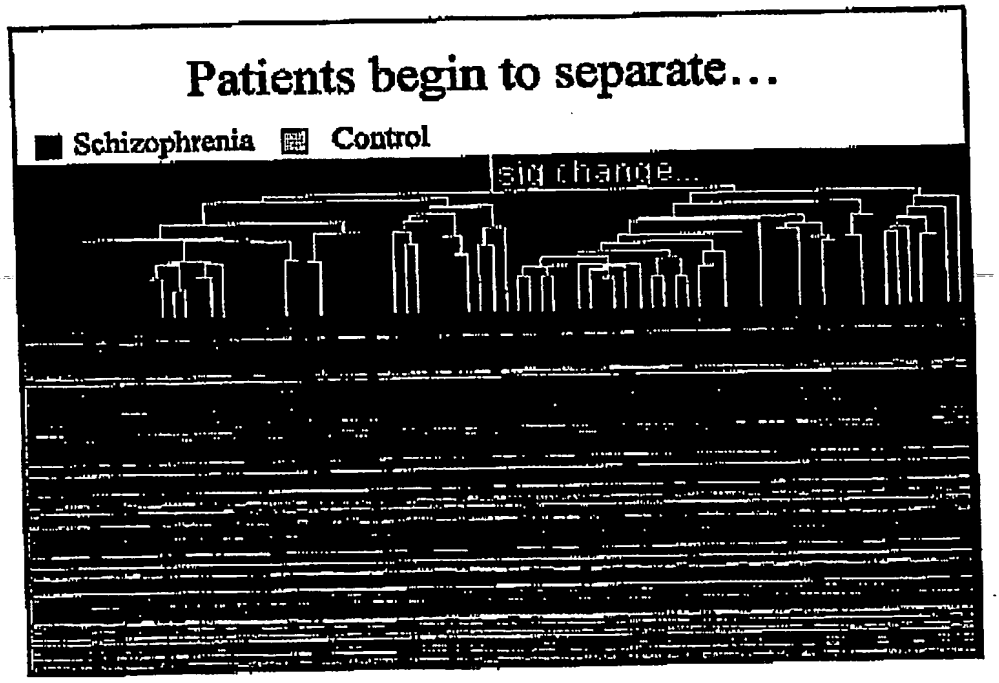
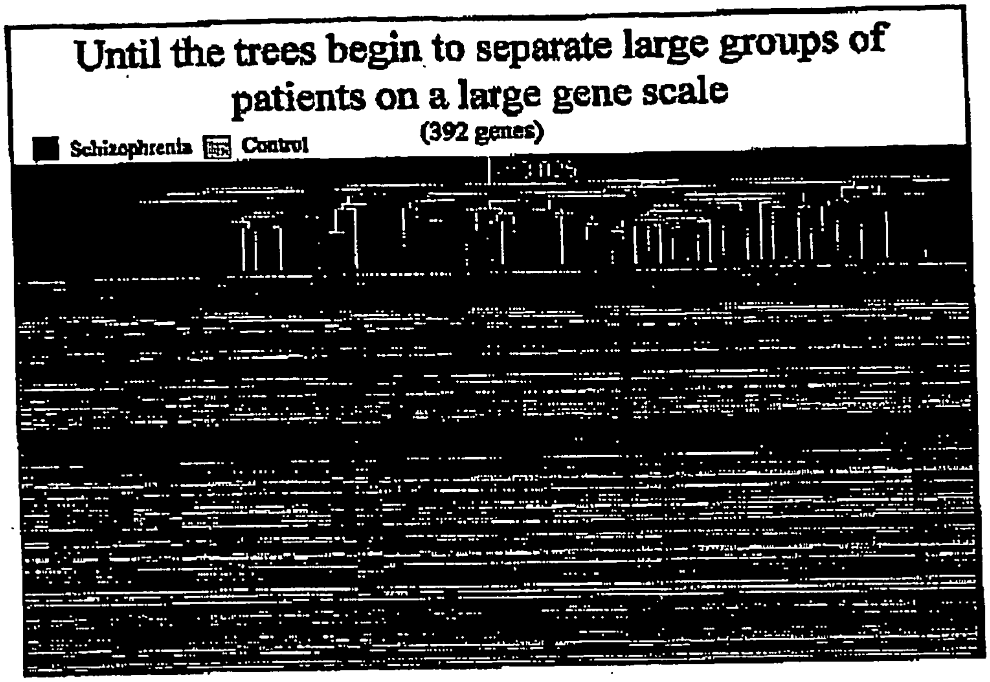

Patients begin to separate...
Schizophrenia
Control
sig change...

Figure 5


Until the trees begin to separate large groups of patients on a large gene scale
(392 genes)
Schizophrenia
Control

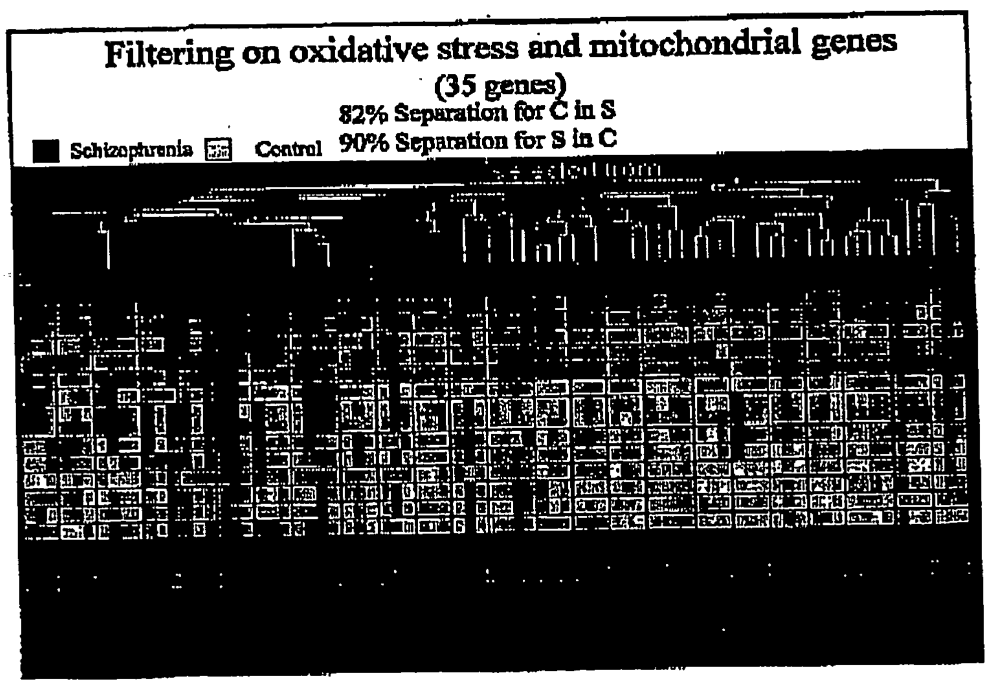

Filtering on oxidative stress and mitochondrial genes
(35 genes)
82% Separation for C in S
90% Separation for S in C
Schizophrenia
Control

Figure 6

Oxidative Buffering